REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 23-33 and 45-48 are in the case.

I. THE OBVIOUSNESS REJECTION

Claims 23-33, 45 and 46 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Salimath *et al*. (US 20030185917; Pub. Date: Oct. 2, 2003) (Salimath) in view of Thibault *et al*. (USP 5099009, Pub. Date: Mar. 24, 1992) (Thibault) and Villa *et al*. (EP 1183014, Pub. Date: March 06, 2002) (Villa). The rejection is respectfully traversed.

As claimed, there is provided an oral pharmaceutical or dietary composition comprising an active ingredient and a soluble or water dispersible dietary fibre. The active ingredient consists of at least one short-chain fatty acid or salt thereof, and the soluble or water dispersible dietary fibre is selected from inulin, dextrin, maltodextrin or derivatives thereof. One or more pharmacologically acceptable excipients are also present. The claimed composition comprises (a) a matrix consisting of lipophilic compounds with a melting point lower than 90°C and optionally amphiphilic compounds in which the active ingredient is at least partially incorporated, (b) an amphiphilic matrix, and (c) an outer hydrophilic matrix in which the lipophilic matrix and the amphiphilic matrix are dispersed. Support for the soluble or water dispersible dietary fibre appears in the specification as originally filed at, for example, page 4, beginning at line 23. No new matter is entered.

An important objective of the present invention is to provide an **oral** composition which acts to release the active ingredient exclusively in the colon, giving rise to a localized **topical** effect **without** absorption in the circulation and/or in the bloodstream (i.e., no systemic effect). The claimed oral composition is able to pass unaltered through the stomach and the small intestine, and to release the active ingredients upon reaching the colonic region.

The claimed invention centers on the surprisingly discovery that the combination of a short-chain fatty acid (SCFA) or salt thereof, and a soluble or water dispersible dietary fibre leads to a significant synergistic effect between these components which, in turn, provides beneficial effects to the patient (see, for example, the present specification at paragraph [0014], Example 4, and Exhibit 1 of the Moro declaration dated July 7, 2011, which is a copy of an experimental report performed under Dr. Moro's direct supervision and control to evaluate the dissolution profile of the compositions of the invention, particularly tablets containing SCFA (calcium butyrate) and inulin). Moreover, the claimed composition, in addition to exhibiting the synergistic effect mentioned above, provides advantages by virtue of being administered orally over prior compositions which are administered rectally. Thus, prior to the present invention, in order to ensure that butyric acid or its salts reached the colon in adequate amount, administration was performed rectally. However, such rectal administration was limited to the distal region of the colon, while not reaching the proximal area, and was accompanied by discomfort to the patient (see, paragraph 0011 of the specification).

By making the claimed composition suitable for oral administration, this ensures the specific local release in the entire colon of the patient, giving rise to a surprising and

significant improvement in the treatment of colonic diseases as, for example, inflammatory bowel disease (IBD) (see specification, for example, paragraphs [0011], [0019], [0020], [0024] to [0026] and the Assisi article submitted herewith via an Information Disclosure Statement). None of the cited art (alone or in any combination) suggests a composition based on SCFAs or salts thereof and soluble or water-dispersible fibres which is able to pass unaltered through the gastro-intestinal tract, releasing locally and specifically in the colon wherein the effect of the active ingredient is topical (with no systemic absorption).

The synergistic effect between the two components of the claimed composition is demonstrated by Example 4 (specification, page 10) which describes a clinical study showing the improved effect obtained by administering a tablet containing the combination of active ingredients according to the invention with respect to the same dosage of the active ingredients taken alone (i.e., the combination of butyric acid + inulin vs. butyric acid alone or inulin alone) in the treatment of inflammatory bowel disease (IBD). The synergism is demonstrated by Table 1 and the Results section. Moreover, it is well known in the art that the profile of compositions cannot be controlled with usual *in vitro* test methods where an enzymatic system is absent. Accordingly, dissolution tests commonly used to verify the release of drugs contained in such compositions are ineffective until a triggering agent (typically an enzyme) is introduced (see Jinhe Li, *et al,* PharmaSciTech, December 2, 2002; 3 (4) article 33 – of record).

The present invention additionally comprises a multi-matrix composition wherein the release of the active ingredient (SCFA) is due to the specific structure of the matrices as recited in claim 23, in which the SCFA is dispersed. No additional triggering

agents or enzymes are necessary to obtain the dissolution of the composition of the invention and the release of the drug. This is demonstrated in the Exhibit to the Rule 132 declaration executed by Luigi Moro of record. The Exhibit is an experimental report describing tests performed by the applicant to evaluate the dissolution profile of the compositions of the invention, particularly tablets containing SCFA (calcium butyrate) and inulin. The test was performed according to the requirement of the USP Pharmacopeia (apparatus II, Jinhe - 3 - Li, *et al.,* PharmaSciTech, December 2, 2002; 3 (4), article 33, referenced above), without adding any triggering agent. The tested tablets showed a characteristic extended dissolution profile due to the specific multi-matrix structure of the product, which can be distributed in different regions of the intestinal tract (see the experimental report and Example 4 of the application). Based on the showing, the Moro declaration concludes that none of the cited prior art discloses or suggests the synergistic technical effect achieved by the present invention, including the control of the release of the active through a specific multimatrix structure of the composition.

Turning to the cited art, Salimath makes no reference to soluble or water-dispersible fibres, nor to such fibres in combination with short-chain fatty acid or salts thereof, as claimed. Salimath clearly does not suggest the invention as claimed.

The Action asserts, with regard to Salimath, that it discloses pectins derived from wheat bran, and are used as alimentary fibres (Action, for example, at page 4-5). However, it is well known that wheat bran, and pectins derived therefrom, are **insoluble** fibres (this is acknowledged on page 4 of the Action). Salimanth in addition discloses the effect of reducing the glomerular filtration rate (paragraph 0024), of reducing urinary

protein excretion (0025) and of treating or controlling diabetic nephropathy (0026). All these effects are systemic effects and require that butyric acid (a SCFA) to be **adsorbed** in circulation and/or in the bloodstream to carry out such physiological functions (see Salimath, background explanation (0002) and the Examples).

In contrast, the technical effect achieved by the presently claimed composition is to ensure that the short chain fatty acid (or salt thereof) and soluble fibre are **not** adsorbed in the bloodstream, to thereby allow their passage through the entire gastro-intestinal tract unchanged and be released exclusively in the colon region, where the combination of the invention acts topically (paragraph [0025]). This effect is achieved according to the invention employing an **oral** composition of SCFA (preferably butyric acid or a salt thereof) and a soluble fibre (preferably inulin) which is able to reach the colonic section largely intact by passing through the stomach and the small intestine without releasing the active ingredients. According to the invention, the short chain fatty acid, or its salt, is **not** systemically absorbed and rather provides exclusively a topical effect solely in the colon (specification, paragraphs [0019]-[0020], [0025]).

Thibault and Villa do not cure the deficiencies of Salimath. Thibault only refers to methods for obtaining soluble fibres from various starting materials, and while Villa reports the possibility of controlling the release of various active ingredients in the gastrointestinal tract (Action, page 6, and paragraph [0001] of the cited document), the release in Villa is in the entire gastrointestinal tract, including the upper part of intestine (ileum and jejunum), and **not solely** in the colon.

In this regard, attention is directed to Assisi *et al*. (see the Information Disclosure Statement submitted herewith) in which the composition of the present invention has

been evaluated (identified as "Zacol NMX"). Assisi states that the composition reached the "..terminal ileum unaltered, where the active ingredient is then gradually released in the cecum, being distributed along the entire colon..." (Assisi: last paragraph of right column, page 232 and first lines of page 233), emphasizing the advantages over the known rectal administration (the method employed to reach the colon prior to the present invention). As is well known, the cecum is the first part of the colon. The study reported in Assisi also demonstrates the advantageous topical effects of the composition of the invention, which also improves the treatment of colonic inflammatory diseases (Assisi, right column of page 234 and final part at page 235).

In light of the above, it is clear that the cited art fails to give rise to a *prima facie* case of obviousness of the claimed composition. Based on the surprising and unexpected synergistic results obtained according to the invention, one of ordinary skill in the art, as of the filing date of the application, would not have been motivated to combine Salimath, Thibault and/or Villa. Even if such a combination had been attempted (this is not admitted), the presently claimed invention would not have resulted or have been rendered obvious thereby, because the cited art does not suggest the combination of soluble or water-dispersible fibres with short-chain fatty acid or salts thereof. Withdrawal of the obviousness rejection of claims 23-33, 45 and 46 over Salimath, Thibault and/or Villa is respectfully requested.

II. AMENDMENTS

Claim 26 has been amended so that it is not a duplicate of claim 46, and new dependent claims have been added directed to the salts calcium butyrate, sodium

butyrate and magnesium butyrate, with preferred one being calcium butyrate. Support appears in the originally filed application, for example, at paragraphs [0012], [0016] and in the Examples. No new matter is entered.

Favorable action is awaited.

Respectfully submitted,

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